Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 146-148, 150-174, 176, 177, 180-203, 233, and 237-244 are pending in the application, with claims 146-148, 176, 177, and 233 being the independent claims.

Claims 146-148, 176 and 177 have been amended by deleting the phrase "and wherein said method treats, alleviates or reduces one or more symptoms of allergic disease." Support for these amendments can be found in the specification, for example, at page 4, lines 3-8 and in Experimental Example 6. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Statement of Substance of Interview

Applicants thank the Examiner for the courtesy of the in-person interview held on August 2, 2010, with Applicants' representative, Timothy J. Shea, Jr., regarding the present application and Office Action. During that interview, Applicants' representative and Examiner discussed the Office Action, pending claims, and cited references. The Examiner indicated that Applicants' reply will be reviewed for determination of allowability. Further to the interview, Applicants provide herein arguments for consideration.

III. The Rejections

A. Rejection #1 Under 35 U.S.C. § 103(a)

Claims 146-148, 150-153, 155-177, 179-183, 185-203, 233, and 237-244 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Murad (U.S. Pat. No. 6,630,163) in view of Endres *et al.* (DE 19758090 A1) and/or Udagawa (JP 61140510 A) and/or Luo *et al.* (CN 1107308 A), Tsuboi *et al.* (JP 02202808 A), Wuthrich (*Clin. Exp. Allergy 8(3)*:241-248), Lukacs *et al.* (U.S. Pat. Appl. No. 2002/0006410 A1), and Capetola *et al.* (U.S. Pat. No. 4,444,780). Applicants respectfully traverse the rejection.

1. Elements of a Prima Facie Case of Obviousness

In order to establish a *prima facie* case of obviousness, (1) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007) *(KSR)*, noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. Quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), the Court stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR v. Teleflex*, 550 U.S. at 735, 82 USPQ2d at 1396.

Applicants maintain that the combination of references cited do not establish a *prima facie* case of obviousness. In particular, the cited references would not provide one of ordinary skill in the art with the requisite reasonable expectation of success in achieving the claimed invention, *i.e.,* methods of reducing IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease via the oral administration of an extract of *Actinidia arguta*. At most, the combination of cited references is an invitation to experiment. However, this is not enough to establish *prima facie* obviousness. Thus, Applicants respectfully request that the rejection be reconsidered and withdrawn.

2. Murad (U.S. Pat. No. 6,630,163)

The Examiner relies on Murad as teaching a method of treating dermatological disorders, including inflammatory dermatoses, with fruit extracts including kiwifruit extract.

However, Murad does not teach that kiwifruit extracts, or any fruit extract for that matter, can successfully treat inflammatory dermatoses. Rather, Murad repeatedly states that the purpose of the fruit extract, is to neutralize free radicals. (*See* Summary of Invention at col. 6, lines 23-29.) For example, Murad states: "The present methods and dermatological agents advantageously manage dermatological conditions, in part by providing antioxidants that are naturally present in fruit extracts. Without wishing to be bound by a theory, *it is believed that these antioxidants facilitate neutralization of free radicals in the skin.*" (*See* Detailed Description at col. 7, lines 49-54.) Murad does not attribute any anti-inflammatory activity to the fruit extract. Instead, when inflammation

is mentioned in Murad, it is always in the context of a separate anti-inflammatory component that is administered in conjunction with the fruit extract: "*The additional pharmaceutical composition may also be an anti-inflammatory component* in an amount sufficient to inhibit or reduce inflammation, an immunity boosting component provided in an amount sufficient to stimulate the patient's immune system response to prevent or facilitate repair of damaged skin . . . ." (*See* Summary of the Invention at col. 6, lines 64 through col. 7, line 2.) Thus, Murad does not teach that fruit extracts have anti-inflammatory activity.

Additionally, Murad does not contain any working examples of kiwifruit extract, or any fruit extract, being used to successfully treat inflammation or any allergic disorder. The first thirteen examples in Murad only disclose the *preparation* of various compositions comprising fruit extracts (none of which include kiwi). Other than Example 14, the application does not disclose any actual experimental results obtained by administration of these compositions. Example 14, the only working example discussing actual experimental results, shows only that a pomegranate extract showed some value in increasing the *antioxidant effect* of certain sunscreens. Murad simply fails to provide any motivation whatsoever to use kiwifruit extracts to treat inflammatory disorders.

Finally, Murad is nothing more than a broad invitation to experiment with the use of fruit extracts in dermatological conditions. Murad mentions a long laundry-list of fruit extracts that purportedly can all be used to treat a laundry list of dermatological disorders. However, the complete lack of experimental data demonstrating the effectiveness of such compositions in treating any disorder other than UV damage,

would lead one of ordinary skill in the art to recognize that Murad is nothing more than an overbroad generalization and invitation to experiment.

Accordingly, one of ordinary skill in the art would not view Murad as providing any reasonable expectation that the claimed kiwifruit extracts could be successfully administered to reduce IgE production, to decrease the serum level of IgG1 and increase the serum level of IgG2a, to decrease Th2 serum cytokines and increase Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease as required by the current claims. Without such a reasonable expectation of success, the *prima facie* case of obviousness must fail.

3. Endres et al. (DE 19758090 A1)

While Endres mentions using *Actinidia arguta* extracts to ***topically*** treat non-allergic inflammatory dermatological conditions (*e.g.,* psoriasis), Endres provides no motivation whatsoever to *orally* administer such extracts for purposes of reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease. Accordingly, Endres fails to cure the deficiencies of Murad.

Additionally, Applicants submit that topical treatments generally do not provide the same type of systemic relief imparted by orally administered therapeutics. In contrast with topical therapeutics that bypass the gastrointestinal system to provide local relief, orally administered therapeutics must pass through the gastrointestinal tract, the intestinal wall and the liver before they are transported via the bloodstream to provide systemic relief.

At page 10 of the Office Action, the Examiner asserts that "Endres teaches the hardy kiwi juice is used in treating psoriasis an allergic inflammatory disease (also see Pegg et al. US 5955463 A col 11 lines 20-25)." It appears that the Examiner is relying on U.S. Pat. No. 5,955,463 ("Pegg") to categorize psoriasis as an allergic disease. Pegg was filed on March 9, 1993. Applicants submit that Pegg does not teach the molecular mechanism underlying psoriasis. Nor does Pegg provide peer-reviewed, scientific references to support the assertion that psoriasis is an allergic disease. Rather, the single sentence in Pegg that the Examiner relies on to support her assertion is a bogus teaching provided by an outdated reference.

In the event that the teachings of two or more prior art references conflict, the M.P.E.P. §2143.01 (Eighth Edition, Rev. August 2007) states that

> [t]he test for obviousness is what the ***combined*** teachings of the references would have suggested to one of ordinary skill in the art, ... Where the teachings of two or more prior art references ***conflict***, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young,* 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991) ....

Id. (emphasis added).

Applicants submitted numerous peer-reviewed, scientific references detailing the underlying mechanism of psoriasis, a non-allergic disease, and distinguishing it from atopic dermatitis, an allergic disease, in their Amendment and Reply dated April 6, 2009, including Nomura, I. *et al., J. Immunol. 171*:3262-3269 (2002), Traub, M. and Marshall, K. *Alt. Med. Rev. 12*:319-330 (2007), Broide, D. and Sriramarao, P., *Immunol. Rev. 179*:163-172 (2002), Leung, D.Y., *Clin. Exp. Immunol. 107 Suppl 1*:25-30 (1997), Ghoreschi, K. and Rocken, M., *Curr. Drug Targets Inflamm. Allergy 3(2)*:193-198

(2004), and Koreck, A. *et al., Clin. Exp. Immunol. 127(1)*:176-182 (2002). The combined teachings of these references would have suggested to a person of ordinary skill in the art at the time the application was filed that the molecular mechanisms underlying psoriasis and allergic disease are different and that a subject with psoriasis would not benefit from a reduction in Th2 serum cytokines or an increase in Th1 serum cytokines, as recited in the pending claims.

Additionally, the volume of peer-reviewed, scientific references supplied by the Applicants regarding the mechanism and categorization of psoriasis outweighs the unsupported and outdated single sentence teaching relied upon by the Examiner. Thus, the combined teachings of these references would have suggested to a person of ordinary skill in the art at the time the application was filed that psoriasis is not an allergic disease and that Endres does not teach decreasing Th2 serum cytokines and increasing Th1 serum cytokines by orally administering an extract of *Actinidia arguta* to a mammal in need thereof.

4. Udagawa (JP 61140510 A)

While Udagawa mentions the use of *Actinidia kolomikta* and *Actinidia polygama* fruit extracts in *cosmetics* and juices as a starting material in food, Udagawa also does not teach orally administering extracts of *Actinidia arguta* to reduce serum IgE, decrease the serum level of IgG1 and increase the serum level of IgG2a, decrease Th2 serum cytokines and increase Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease in a mammal in need thereof. Accordingly, Udagawa does not cure the deficiencies of Murad and Endres.

5. Luo et al. (CN 1107308 A)

Luo generally discusses the use of kiwi fruit extracts and beverages for the treatment of illness, but does not specifically mention *Actinidia arguta* extracts or methods for *reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a,* or *decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease* by *orally* administering an *Actinidia arguta* extract to a mammal in need thereof. As such, the references combined fail to provide a reasonable expectation for successfully reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease.

6. Tsuboi et al. (JP 02202808 A); Wuthrich (Clin. &. Exp. Allergy 8:241-248); Lukacs et al. (U.S. Pat. Appl. Publ. No. 2002/0006410); and Capetola et al. (U.S. Pat. No. 4,444,780 A)

The Examiner has additionally cited Wuthrich, Lukacs and Capetola. Wuthrich describes increased IgE production associated with atopic dermatitis. Lukacs discusses what is already known in the art by way of T_H1/T_H2 immune response mechanisms. Capetola describes a relationship between histamine release and edema and atopic dermatitis. However, these documents do not cure the deficiencies of Murad. They are cited to show the connection between atopic dermatitis and certain immune responses. But as noted above, Murad does not provide any reasonable expectation of success that kiwifruit extracts can be successfully used to treat dermatological conditions other than

UV damage. The examiner is not permitted to use hindsight reconstruction, based on the teachings of Applicants' disclosure, to make a case for obviousness.

For the above reasons, the Examiner has failed to establish a *prima facie* case of obviousness, and the rejection must be withdrawn.

7. The Uncontroverted Evidence of Unexpected Results of Presently Claimed Methods Rebuts Any Prima Facie Case of Obviousness

Even if it is assumed, for the sake of argument, that the cited references establish a *prima facie* case of obviousness, Applicants have submitted herewith experimental data that clearly demonstrates the unexpected superiority of the extract of *Actinidia arguta* compared to commercial kiwifruit in the claimed therapeutic uses. This evidence rebuts any *prima facie* case of obviousness.

Applicants submit that in view of the references cited by the Examiner one of ordinary skill in the art would expect to observe similar therapeutic efficacy regardless of the type of kiwifruit used. Surprisingly, Applicants experimental results demonstrate that the extract of *Actinidia arguta* is clearly superior to a commercial kiwifruit (*Actinidia deliciosa*) extract in reducing IgE and IL-4 production.

Applicants attach herewith the Declaration of Dr. Sunyoung Kim (hereinafter "the Kim Declaration"), which provides a side-by-side comparison of the effects of extracts of *Actinidia arguta* and *Actinidia deliciosa* on IgE production in U266B1 cells and IL-4 production in ovalbumin (OVA)-sensitized splenocytes from BALB/c mice. The data presented in Exhibit B and discussed in the Kim Declaration, demonstrate that the *Actinidia arguta* extract is more potent than the *Actinidia deliciosa* extract at inhibiting IgE production. Additionally, the data presented in Exhibit C and discussed in

the Kim Declaration, demonstrate that the *Actinidia arguta* extract is more potent than the *Actinidia deliciosa* extract at decreasing IL-4 (Th2 cytokine). Applicants submit that nothing in the cited reference would lead one of skill in the art to expect the superior potency of the extract of *Actinidia arguta* in reducing IgE and IL-4 production. Accordingly, Dr. Kim's Declaration and the experimental data are sufficient to rebut the *prima facie* case of obviousness.

B. Rejection #2 Under 35 U.S.C. § 103(a)

Claims 154 and 184 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Murad in view of Endres and/or Udagawa and/or Luo, Tsuboi, Wuthrich, Lukacs, and Capetola, and further in view of Suzuki *et al.* (U.S. Publ. No. 2002/0054923 A1). Applicants respectfully traverse the rejection.

Pending claim 154 depends from claim 151, which in turn depends from independent claims 146-148. Accordingly, claim 154 incorporates the limitations of claims 146-148 and 151. Pending claim 184 depends from claim 181, which in turn depends from independent claims 176 and 177. Accordingly, claim 184 incorporates the limitations of claims 176, 177, and 181. As discussed above, Murad, Endres, Udagawa, and Luo do not teach each and every claim limitation of the pending claims. Applicants submit that Tsuboi, Wuthrich, Lukacs, Capetola, and Suzuki do not disclose methods for reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, or decreasing Th2 serum cytokines and increasing Th1 serum cytokines by orally administering *Actinidia arguta* extracts as recited in independent claims 146-148, 176, and 177. Suzuki merely discusses commercial kiwifruit extract compositions. As such, Applicants submit that no reason is provided, either in the

references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at methods for reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, or decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease by orally administering *Actinidia arguta* extracts simply by combining the Murad, Endres, Luo, Tsuboi, Wuthrich, Lukacs, Capetola, and Suzuki references. Moreover, a skilled person in the art would not have had a reasonable expectation of achieving the desired therapeutic results based solely on the cited references. As such, Applicants submit that the Examiner has failed to make a *prima facie* case of obviousness.

Accordingly, it is respectfully requested that the rejection of pending claims 154 and 184 under 35 U.S.C. § 103(a), as allegedly being obvious, be reconsidered and withdrawn.

Even assuming, *arguendo*, that a *prima facie* case of obviousness had been established, which it had not, the unexpected superior results achieved using *Actinidia arguta* extracts over Murad's commercial kiwifruit extracts for reducing serum IgE production and decreasing Th2 serum cytokines and increasing Th1 serum cytokines as discussed above, is sufficient to rebut the *prima facie* case of obviousness.

C. Rejections #3 Under 35 U.S.C. § 103(a)

Claims 146-148, 150-153, 155-177, 179-183, 185-203, 233, and 237-244 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Motohashi N., *West*

Aust. Nut and Tree Crops Assoc. 16:48-59 (1991), Tsuboi, Wuthrich, Lukacs, and Capetola. Applicants respectfully traverse the rejection.

*1. Motohashi (West Aust. Nut and Tree Crops Assoc. **16:48-59** (1991))*

Motohashi mentions that *Actinidia eriantha*, a non-hardy kiwifruit plant species, can be used to treat dermatitis, an allergic disease. However, Motohashi fails to describe which parts of the *Actinidia eriantha* plant are useful for treating dermatitis or how such treatment is administered. Additionally, Motohashi fails to describe extracts of *Actinidia eriantha*. While Motohashi also mentions that *Actinidia chinensis* and *Actinidia callosa* can be used to treat edema, neither of these kiwifruit species are hardy kiwifruit species. Thus, Motohashi fails to disclose extracts of *Actinidia arguta* for reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease. As such, the reference does not teach all of the claim limitations of any of the pending claims.

2. Tsuboi, Wuthrich, Lukacs, and Capetola

As mentioned above, Tsuboi, Wuthrich, Lukacs, and Capetola do not disclose methods for reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease by orally administering *Actinidia arguta* extracts as recited in independent claims 146-148, 176, and 177. Therefore, none of these references cure the deficiencies of Motohashi. Also as explained above, the claimed methods are non-obvious because the cited references (1) do not teach (individually or in combination)

methods for reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease by orally administering *Actinidia arguta* extracts to a mammal in need thereof; (2) do not provide one of skill in the art with a reason to modify the references to arrive at the claimed invention; and (3) do not provide a reasonable expectation of success. As such, Applicants submit that with regard to the pending claims the Examiner has failed to make a *prima facie* case of obviousness.

Accordingly, it is respectfully requested that the rejection of pending claims 146-148, 150-153, 155-174, 176, 177, 180-183, 185-203, 233, and 237-244 under 35 U.S.C. § 103(a), as allegedly being obvious, be reconsidered and withdrawn.

D. Rejection #4 Under 35 U.S.C. § 103(a)

Claims 154 and 184 are rejected under 35 U.S.C. § 103(a), as allegedly being obvious over Motohashi in view of Tsuboi, Wuthrick, Lukacs, and Capetola, and further in view of Suzuki. Applicants respectfully traverse the rejection.

Pending claim 154 incorporates the limitations of claims 146-148 and 151. Pending claim 184 incorporates the limitations of claims 176, 177, and 181. As discussed above, Motohashi does not teach each and every claim limitation of the pending claims. Additionally, none of the references teach the mechanism underlying allergic disease. Applicants submit that Tsuboi, Wuthrich, Lukacs, Capetola, and Suzuki also do not disclose methods for reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one

or more symptoms of allergic disease via the oral administration of an *Actinidia arguta* extract as recited in independent claims 146-148, 176, 177, and 233. Suzuki merely discusses commercial kiwifruit extract compositions. As such, Applicants submit that no reason is provided, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings to arrive at methods for reducing serum IgE production, decreasing the serum level of IgG1 and increasing the serum level of IgG2a, decreasing Th2 serum cytokines and increasing Th1 serum cytokines, or methods for treating, alleviating, or reducing one or more symptoms of allergic disease via the oral administration of an *Actinidia arguta* extract simply by combining the Motohashi, Tsuboi, Wuthrich, Lukacs, Capetola, and Suzuki references. Moreover, a skilled person in the art would not have had a reasonable expectation of achieving the desired therapeutic results based solely on the cited references. As such, Applicants submit that the Examiner has failed to make a *prima facie* case of obviousness.

Accordingly, it is respectfully requested that the rejection of pending claims 154 and 184 under 35 U.S.C. § 103(a), as allegedly being obvious, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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